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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/634,039
Filing Date	April 17, 1996
First Named Inventor	Denis P. Snider
Art Unit	1644
Examiner Name	Gerald R. Ewoldt
Total Number of Pages in This Submission	
Attorney Docket Number	1038-588 MIS:jb

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*:
  1. **Response to Non-compliance**
  2. **Amended Appeal Brief**
  3. **Postcard**

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	**Michael I. Stewart (Reg. No. 24,973)**
Signature	
Date	**December 8, 2003**

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria,VA 22313-1450 on the

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Writer's Ext. 239

E-mail: **mistewart@sim-mcburney.com**

December 8, 2003

Via Courier

Mail Stop AF
Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
U.S.A.

Dear Sir:

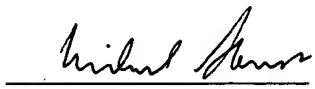
RE: US Patent Application No: 08/634,039
Applicant: Denis P. Snider
Filed: April 17, 1996
Examiner: Gerald R. Ewoldt
Group No.: 1644
Title: METHODS AND COMPOSITIONS CONTAINING ANTIGENS HAVING A TARGETING MOIETY SPECIFIC FOR ANTIGEN PRESENTING CELLS FOR INTRANASAL IMMUNIZATION

In response to the Communication dated November 17, 2003 concerning the Notice of Non-compliance with 37 CFR 1.192(c).

The Notice indicated that the brief does not contain a concise explanation of the claimed invention, referring to the specification by pages and lines number. A concise explanation of the invention appears in the Brief. An Amended Appeal Brief in triplicate now is enclosed with the indication of the page and line number where the invention is described.

It is submitted that the Brief now fully complies with 37 CFR 1.192(c).

Yours very truly,



Michael I. Stewart
Reg. No. 24,973

Enclosure(s)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Denis P. Snider
Appl'n. No.	:	08/634,039
Filed	:	April 17, 1996
Title	:	METHODS AND COMPOSITIONS CONTAINING ANTIGENS HAVING A TARGETING MOIETY SPECIFIC FOR ANTIGEN PRESENTING CELLS FOR INTRANASAL IMMUNIZATION
Grp./A.U.	:	1644
Examiner	:	Gerald R. Ewoldt
Docket No.	:	1038-588 MIS:jb
Date	:	December 8, 2003

AMENDED APPEAL BRIEF

BY COURIER

Mail Stop AF
Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
U.S.A.

Dear Sir:

1. Introduction

This Appeal Brief is submitted pursuant to applicant's appeal of the Final Rejection dated August 6, 2002. Three copies of this Appeal Brief are submitted. The enclosed cheque includes the prescribed fee for an Appeal Brief.

2. Extension of Time

Petition is hereby made to provisions of 37 CFR 1.136(a) for an extension of five months of the period for submission of this Appeal Brief. The enclosed cheque includes the prescribed fee for the extension of time.

3. Real Party of Interest

The real party of interest is McMaster University by virtue of a deed of Assignment from the inventor recorded at Reel/frame 8272/0624.

4. Related Appeals and Interferences

There are no related appeals and interferences known to the appellant, appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

5. Status of Claims

This application was filed with claims 1 to 9. Claim 9 is cancelled by an Amendment filed simultaneously herewith. The claims appealed appears in the Appendix hereto.

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An Amendment after Final Action is being submitted simultaneously herewith and has not yet been acted on.

7. Summary of Invention

The invention is concerned with a method of generating an immune response to an antigen in a host by intranasal administration to the host of an antigen coupled to a targeting moiety specific for unique structures of antigen-presenting cells. (Page 4, lines 2 to 11)

8. Issues

The issues to be determined in this appear are:

1. Rejection of claims 1 to 9 under 35 USC 103(a) as being unpatentable over Estrada et al in view of McDermott et al and Hameleers et al.

2. Rejection of claims 1 to 9 under 35 USC 103(a) as being unpatentable over Estrada et al in view of McDermott et al and Hameleers et al and US Patent No. 4,228,795.

9. Grouping of Claims

Claims 1 to 8 stand or fall together. Claim 9 has been cancelled.

10. Argument

(a) Background to the Invention

Current theories of immunology suggest that, in order to provide a potent antibody response, an antigen must be seen by both B cells, which subsequently develop into the antibody producing cells, and also by helper T-cells, which provide growth and differentiation signals to the antigen specific B-cells. Helper T-cells recognize the antigen on the surface of antigen- presenting cells (APC) in association with Class II major histocompatibility complex (MHC) gene products.

There are significant advantages in using proteins and peptides and other antigens such as polysaccharides derived from proteins of infectious organisms as components in subunit vaccines. The search for such suitable subunits constitutes a very active area of both present and past research. Advances in techniques of recombinant DNA manipulations, antigen and protein purification, peptide synthesis and cellular immunology have greatly assisted in this endeavour. However, a problem in the use of such materials as vaccines has been the relatively poor *in-vivo* immunogenicity of most protein subunits, polysaccharides and peptides. Generally, the immune response to vaccine preparations is enhanced by the use of adjuvants. However, the only currently licensed adjuvants for use in humans are aluminum hydroxide and aluminum phosphate, collectively termed alum, which is limited in its effectiveness as a potent adjuvant. There is thus a need for new adjuvants with the desired efficacy and safety profiles.

Several adjuvants, such as Freund's Complete Adjuvant (FCA), syntex and QS21, have been used in animals. A novel way of engaging both the B and T cell components of an immune response has been described, which uses anti-class II monoclonal antibodies (mabs) coupled to antigens to target class II bearing antigen presenting cells (APC's). Experiments carried out *in-vivo* in rodents and rabbits using this technology, have demonstrated convincing proof of enhancement in immunogenicity of antigens, in the absence of conventional adjuvants. Other cell surface markers such as Surface Immunoglobulin (sIg), and MHC class I, have been used to achieve targeting to APC's.

(b) The Invention

As noted above, the invention is a method of generating an immune response to an antigen in a host, including a human host, by intranasal administration to the host of an antigen coupled, preferably by a heterobifunctional linking molecule, to a targeting moiety specific for surface structures of antigen-presenting cells, preferably a monoclonal antibody. As noted above, antigen coupled to targeting moieties have previously been used to generate an immune response to the antigen by parenteral administration to a host. However, there was no reason to believe that the antibody conjugate would bind specifically to the nasal passages or be taken up by the epithelium having regard to the structures of such epithelial surfaces.

(c) Rejection of claims 1 to 9 under 35 USC 103 over Estrada et al in view of McDermott et al and Hameleers et al

Estrada et al is concerned with a technique for immunization of the intestinal tract of mice using protein antigen bound to antibodies specific for murine MHC class II molecules. The specific conjugates, consisting of hen avidin (AV) or hen egg lysozyme (HEL) covalently conjugated to anti-MHC-II antibodies, are administered orally (p.o.) or by direct intraduodenal (i.d.) injection into the intestinal lumen of mice. Applicants invention is not concerned with oral or intraduodenal administration of the antigen-antibody conjugates, but rather effects administration intranasally.

The results which are described in Estrada et al (page 904, right hand column) refer to obtaining a weak and inconsistent production of intestinal IgA-antibody. The results also recite that serum IgG and IgA response may be opitmized by high doses of antigen. Further, a significant mouse-to mouse variation in antibody response was apparent within any immunization group, leading to a study of direct injection into the duodenum.

The last paragraph of the article (p. 906, right hand column) alludes to further studies but there is no subsequent paper by this group relating to any further experiments. It must be construed from this fact that the mucosal administration procedure described in Estrada et al was not sufficiently promising to merit further work and the approach simply was abandoned.

It is submitted that, having regard to the work described in Estrada et al, a person skilled in the art would have no reason to believe that the antigen-antibody conjugate would bind specifically to the epithelium of nasal passages or be taken up by the epithelium.

The antibodies used in applicants experimentation have speciality for class II MHC molecules expressed by antigen presenting cells. These class II molecules are only poorly expressed by non-inflamed nasal epithetial cells in young rodents, as described in the Hameleers et al reference, Cell and Tissue Res. 256, p431-438 (1989), of record herein, and different from the Hameleers reference relied on by the Examiner. In addition, there is no evidence that MHC class II molecules are expressed on the external membrane (apical surface) of rodent nasal epithelical cells. Available immunohistochemistry suggests only intracellular localization of class II MHC in the rodent nasal epithelium and those published results cannot define apical expression, as described in the Koornstra et al, Acta Otolaryngol., 113, 660-667 (1993), of record herein.

With respect to these literature references, the Examiner stated in the Final Action of April 2, 2001 that:

> ".... the references were never submitted with any reply by Applicant nor were the references ever made of record in an IDS or on a Form PTO-892."

The applicants had submitted copies of those references and some additional references with a response filed June 5, 2000 along with a PTO-1449 listing the references. The next communication from the Office, the Office Action of August 22, 2000, appended the PTO-1449, initialled by the Examiner as having been considered. A copy of that document is enclosed for convenience.

Accordingly, it is submitted that it is unobvious that monoclonal antibody-antigen conjugates applied to the epithelical surfaces of the nasal passages would be able to reach circulation or even the underlying lymphoid tissue of the epithelium in substantial quantity and produce an immune response to the antigen. The applicant has demonstrated the provision of such an immune response. A person skilled in the art would understand that the epithetial layers of the nasal passages have tight junctions and that large molecules, such as antibodies and conjugates, do not pass through the epithelium, except with only poor efficiency.

Having regard to the work described by Estrada et al, discussed above, and the knowledge of the art, it is submitted that applicants results are surprising.

It is submitted that the secondary references do not remedy the defects of Estrada et al. McDermott et al is a discussion of immunity in the respiratory tract, which possesses lymphoid aggregates similar to the Peyer's patches of the intestinal tract.

Hameleers et al describes that nasal administration of thymus-dependent keyhole limpet haemocyanin (KLH) induced production of IgA and IgG antibodies to the trinitrophenylated (TNP) antigens. The immunogen was administered in the form of liquid droplets.

It is submitted that there is no motivation provided by the results reported in Estrada et al for any expectation of success in achieving an immune response utilizing immunotargeting by intranasal administration of an antigen coupled to a targeting moiety specific for surface structures of antigen-presenting cells.

In the Final Action, the Examiner gives the reason for rejection is:

> "... for the reasons of record as set forth in Paper No. 28, mailed 5/24/02"

Paper No. 28 is dated April 27, 2001 and it is assumed the Examiner is in error.

The Examiner expressed the view in the Final Action of April 27, 2001, that:

> "It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to immunize a subject according to the manner of Hameleers et al substituting the KLH carrier with an anti-MHC class II antibody as taught by Estrada et al. One would have been motivated to make the substitution with a reasonable expectation of success based upon the teachings of McDermott et al that the BALT of the respiratory tract is functionally similar to the PP of the intestines and the teachings of Estrada et al that the antibody conjugates specifically taught the antigen presenting cells in the intestine."

The BALT to which McDermott et al refers is not located in the nasal passages and hence there is no motivation provided. Applicants claims are specifically directed to intranasal administration to the epithelical surfaces in the nasal passages.

Having regard to the above, it is submitted that the Examiner is in error in rejecting claims 1 to 9 under 35 USC 103(a) as being unpatentable over Estrada et al in view of McDermott et al and Hameleers et al.

(d) Rejection of claims 1 to 9 under 35 USC 103 over Estrada et al in view of McDermott et al and Hameleers et al and US Patent No. 4,228,795

It is submitted that this rejection is moot in view of deletion of claim 9.

11. Summary

In summary, it is submitted that the rejection of claims 1 to 8 under 35 USC 103(a) as being unpatentable over Estrada et al in view of McDermott et al and Hameleers et al, should be REVERSED.

Respectfully submitted,

Michael I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada,
(416) 595-1155
FAX No. (416) 595-1163

APPENDIX

CLAIMS APPEALED

1. A method of generating an immune response to an antigen in a host, which comprises:

intranasally administering to said host an antigen coupled to a targeting moiety specific for surface structures of antigen-presenting cells.

2. The method of claim 1 wherein said antigen-presenting cells are selected from the group consisting of class I or class II major histocompatibility expressing cells (MHC), B-cells, T-cells, professional antigen-presenting cells including dendritic cells, and $CD4^+$ cells.

3. The method of claim 2 wherein the targeting moiety is a monoclonal antibody or a fragment thereof.

4. The method of claim 3 wherein the antigen is a protein, peptide, carbohydrate or ligand.

5. The method of claim 4 wherein the antigen is derived from a pathogen and said immune response is a protective immune response against disease caused by said pathogen.

6. The method of claim 5 wherein the immune response is an IgG or an IgA immune response.

7. The method of claim 5 wherein the host is a human host.

8. The method of claim 1 wherein said antigen is coupled to said targeting moiety through a heterobifunctional linking molecule.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Appl'n. No.	:	08/634,039
Filed	:	April 17, 1996
Title	:	METHODS AND COMPOSITIONS CONTAINING ANTIGENS HAVING A TARGETING MOIETY SPECIFIC FOR ANTIGEN PRESENTING CELLS FOR INTRANASAL IMMUNIZATION
Grp./A.U.	:	1644
Examiner	:	Gerald R. Ewoldt
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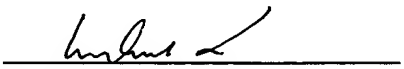
Respectfully submitted,



Michael I. Stewart
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8. The method of claim 1 wherein said antigen is coupled to said targeting moiety through a heterobifunctional linking molecule.